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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/623,548 | 09/05/2000 | Dominique P. Bridon | REDC-2110-USA | 4825 |

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| EXAMINER |
|---|
| DESAI, ANAND U |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/623,548 | BRIDON ET AL. | |
| | Examiner | Art Unit | |
| | Anand U Desai | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *26-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-32 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6,7*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Priority*

1. Receipt is acknowledged of papers filed under 35 U.S.C. 119 (a)-(d) based on an application filed in U.S.A. on May 17, 2000. Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of any foreign application. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date.

### *Specification*

2. The disclosure is objected to because of the following informalities:

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

4. Line 16 of abstract "protecting said peptide".

5. The word count is over 150 words in length.

6. The disclosure is objected to because of the following informalities:

7. The specification on pages 10 and 13, both line 20, the line has a typographical error. The number "2" appears to be intended to be "3" as stated in amended claims.

Appropriate correction is required.

***Claim Objections***

8. As filed, there is no claim 9. Under 37 CFR 1.126, claims 10-26 (as originally filed) and the dependencies have been renumbered as claims 9 to 25 respectively. The amendment filed 5 Mar 2002, is noted as canceling claims 1-26 (renumbered as 1-25) and presenting claims 27-38. Claims 27-38 and the dependencies have also been renumbered as claim 26-37 under 37 CFR 1.126. Consequently claims 26-37 are pending.

9. Claim 35 is objected to because of the following informalities: There is a typographical error. There is an unwanted semi-colon ";" between the word "an" and "amino". Appropriate correction is required.

***Double Patenting***

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 26-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9, and 10 of U.S. Patent No. 6,329,336. Although the conflicting claims are not identical, they are not patentably distinct from each other because Bridon et al., U.S. Patent No. 6,329,336 claims a method of coupling a therapeutic peptide with a reactive group, wherein the reactive group is selected from the group consisting of succinimidyl and maleimido groups which reacts with amino groups, hydroxyl groups or thiol groups on blood components to form covalent bonds with a blood component in vivo, thereby forming a modified peptide having an in vivo half-life longer than the in vivo half-life of the unmodified peptide (claim 9, 10 column 68, lines 30-36; **claims 26-37**).

### *Claim Rejections - 35 USC § 112*

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of synthesizing a modified therapeutic peptide and coupling a succinimidyl-containing reactive group, does not reasonably provide enablement for synthesizing all therapeutic peptides with all reactive groups.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

1.) The nature of the invention: the invention is drawn to methods of synthesizing therapeutic peptide conjugates by attaching reactive groups to the peptide and stabilizing the peptide against peptidases. Such methods are complex in nature.

2.) The breadth of the claims: the claims are broad in that any modified therapeutic peptide is suggested to be synthesized, which is capable of forming a peptidase-stabilized therapeutic peptide conjugate.

3.) Synthesis of polypeptides and covalently linking a reactive group, such as succinimidyl- and maleimido-containing groups, to the polypeptide is predictable. The linked reactive group on the therapeutic peptide can be covalently coupled with the amino, hydroxy, or thiol groups on blood components, but the biological function of a coupled complex is unpredictable. Knusli et al. has shown modification in biological activity upon polyethylene glycol modification of granulocyte-macrophage colony stimulating factor (see Knusli C., et al., *Brit. J. Heamatol.*, 82:654-663 (1992)).

4.) The process of making and using the therapeutic peptide conjugate presented in the specification are not explained in detail for therapeutic peptides whose function is not completely understood, such as C-type natriuretic peptide identified in the specification, and as such any variability in results are not discussed.

5.) The working examples of modified therapeutic peptides do not encompass all types of therapeutic peptides such as C-type natriuretic peptide described in the specifications. The identification of a less therapeutic region on a peptide, where the reactive group should be conjugated, whose function is not completely understood would be difficult.

6.) There is a large quantity of experimentation necessary to determine the biological activity for all the modified therapeutic peptide conjugates described in the specification. The therapeutically less active region of peptides described in the specification would have to be known for conjugation of reactive groups.

7.) The state of the art has demonstrated the preparation and method of use of modified polypeptides for increased biological activity (U.S. Patent 5,580,853, Sytkowski).

8.) In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a doctoral scientist with several years of experience in the art. As the cited art would point to, even with a level of skill in the art which is of a doctoral scientist, predictability of the results is not invariable. In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

***Claim Rejections - 35 USC § 102***

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 26(a), 27-32, and 35-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Ezrin, U.S. Patent 6,500,918 (Effective filing date May 17, 1999). Ezrin teaches the conjugation of antinociceptive agents to blood components via a reactive group. Specifically, Applicants are referred to examples 1, 5, 6 and 8.

In example 1, Ezrin et al. synthesized 13 amino acid Dynorphin A (1-13) from the C-terminus using an automatic peptide synthesizer see the order of sequentially added amino acids and compare to SEQ ID NO: 2. Maleimidoproprionic acid (MPA) was coupled to the C-terminal lysine using HBTU/HOBt/DIEA activation in DMF. In example 6, this conjugate was reacted with human serum albumin (HSA), which is a blood component. The in vivo half life of this dynorphin:HSA was increased as demonstrated by a sustained duration of action in example 8; Thus, the dynorphin:HSA was peptidase-stabilized.

Therefore, Ezrin et al. teach a method for synthesizing a modified therapeutic protein that is a peptidase stabilized conjugate. The dynorphin A is a therapeutic peptide that is a antinociceptive agent and is a 13 amino acid peptide having an amino acid length

between 3 and 50 amino acids. Dynorphin A has a N terminal amino acid, a C terminal amino acid, and an active and a less active region. Dynorphin A does not comprise a cysteine (cys) (**claim 32**) and it was synthesized from the C terminal (**claim 34**) and coupled to a reactive group directly and to the C terminal lysine (**claim 30, 31, 36, 37**). This reactive group forms covalent bonds with the blood component HSA at amino, hydroxy, and thiol groups (column 3, line 40-41; **claim 26a**). The reactive agent was maleimidoproprionic acid, a maleimido-containing group (**claim 27, 29, 35**). Because the Dynorphin:HSA retained activity, the reactive group was coupled to a less active site in dynorphin (**claim 28**)

In example 5 Ezrin et al. synthesized 16 amino acid Dynorphin A (2-17) from the C-terminus using an automatic peptide synthesizer see the order of sequentially added amino acids and compare to SEQ ID NO: 7. Maleimidoproprionic acid (MPA) was coupled to the N-terminal glycine using HBTU/HOBt/DIEA activation in DMF. In example 6, this conjugate was reacted with human serum albumin (HSA), which is a blood component. The in vivo half life of this dynorphin:HSA was increased as demonstrated by a sustained duration of action in example 8; Thus, the dynorphin:HSA was peptidase-stabilized.

Therefore, Ezrin et al. teach a method for synthesizing a modified therapeutic protein that is a peptidase stabilized conjugate. The dynorphin A is a therapeutic peptide that is an antinociceptive agent and is a 16 amino acid peptide having an amino acid length between 3 and 50 amino acids. Dynorphin A has a N terminal amino acid, a C terminal amino acid, and an active and a less active region. Dynorphin A does not comprise a cysteine (cys) (**claim 32**) and it was synthesized from the C terminal (**claim**

**34**) and coupled to a reactive group directly and to the N terminal glycine. This reactive group forms covalent bonds with the blood component HSA at amino, hydroxy, and thiol groups (column 3, line 40-41; **claim 26a**). The reactive agent was maleimidoproprionic acid, a maleimido-containing group (**claim 27, 29, 35**).. Because the Dynorphin:HSA retained activity, the reactive group was coupled to a less active site in dynorphin (**claim 28**).

***Claim Rejections - 35 USC § 103***

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ezrin et al. (U.S. Patent 6,500,918, Effective filing date May 17, 1999). The teachings of Ezrin et al. are set forth above. While Ezrin et al. exemplify the use of a maleimido containing group as the reactive group, Ezrin et al. state that N-hydroxy succinimidyl, a succinimidyl containing group, is also a most convenient reactive group that shows like function with maleimido containing groups (column 3, line 44-46). Therefore, it would have been obvious to person having ordinary skill in the art to substitue succinimidyl for maleimido because Ezrin et al. state that succinimidyl is a reactive group that functions like maleimido and maybe employed as this linking group. Because succinimidyl and maleimido share like properties, it is predictable that succinimidyl can be coupled to

dynorphin and stabilized this peptide because Ezrin et al. demonstrated that maleimido stabilized dynorphin (**claim 26, 27**).

**Art of interest**

Pouletty et al. (U.S. Patent 5,612,034) teaches a method of conjugating a therapeutic polypeptide (column 5, lines 14-16) with a reactive group, such as bis-sulfosuccinimidyl suberate, and N-y-maleimidobutyryloxysuccinimide ester (column 3, lines 15-24), to blood components with amino groups, carboxyl groups, and thiol groups (column 2, lines 15-59). The therapeutic polypeptide, which is covalently bonded to a blood component, is maintained in the host blood stream for the lifetime of the blood component, to provide a substantially extended lifetime for the therapeutic polypeptide (column 1, line 54 through column 2, line 17, see also column 5, lines 9-26).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U Desai whose telephone number is (703) 305-4443. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

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August 22, 2003

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600